## REMARKS

In view of the comments which follow, and pursuant to 37 CFR §1.111, reconsideration of the Official Action of November 21, 2005 is respectfully requested by Applicants.

Claim 1 has been amended to clarify that it is the final suspension/combination of beads and binding partner that has a pH of 10.5 to 12.5. Support for the amendment is found in the specification in Examples 1 and 2 (paragraphs 45 and 46) where pH adjustment is performed after combining microparticles and protein. No new matter has been added.

The drawings have been amended by adding "Figure x" to each sheet and to improve upon the legibility of the axis labeling. No new matter has been added.

Claims 1-3 and 5 remain pending for examination.

Objection to drawings

The drawings submitted by Applicants on October 6, 2005, have not been entered because they were not identified as "Replacement sheet" or "New Sheet" as required by 37 CFR §1.121(d).

The correctly identified drawings were submitted by Applicants on January 20, 2006, in response to the office action of November 21, 2005. However, the examiner did not specify whether they were entered or not. Thus, in response to the Notice of Non-compliant Amendment mailed 10/14/05 and the examiner's objection, Applicants are again re-submitting replacement drawing sheets concommittantly herewith that correct the deficiencies noted by the examiner, and they respectfully request the examiner's reconsideration and entry of the replacement drawings.

Rejections under 35 USC §112, second paragraph

Claims 1-3 and 5 have been rejected under 35 USC §112, second paragraph, for their recitation of "the combination" in part (a).

Claim 1 (and consequently claims 2, 3, and 5 depending therefrom) have now been amended to clarify that it is the final suspension/combination of beads and binding partner that has a pH of 10.5 to 12.5. Support for the amendment is found in the specification in Examples 1 and 2 (paragraphs 45 and 46) where pH adjustment is performed after combining microparticles and protein.

The examiner's reconsideration of the rejection under 35 USC §112, second paragraph, is respectfully requested by Applicants.

Rejections under 35 USC §103 (a)

Claim 1 been rejected under 35 USC §103 (a) as being unpatentable over Vaynberg et al., *Biomacromolecules 1*:466-472, 2000 (hereinafter "Vaynberg") as evidenced by Bocquier et al., *Structure 7*:1451-1460, 1999 (hereinafter "Bocquier") and Bohidar, *International Journal of Biological Macromolecules 23*:1-6, 1998 (hereinafter "Bohidar"). The examiner argues that Vaynberg teaches a method for producing protein-coated polystyrene microparticles that includes the steps of combining a suspension (colloid) of uncoated microparticles with a polymerized protein that is a member of a bioaffinity binding pair (gelatin), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption and separating the non-adsorbed protein from the protein-coated microparticles (by centrifugation). Bocquier is cited as evidence that protein gelatin is a partner of a bioaffinity binding pair as it binds fibronectin, and Bohidar is cited as evidence that gelatin has a size within the recited range of 10 nm to 300 nm.

Claims 2, 3, and 5 have additionally been rejected based upon Vaynberg as evidenced by Bocquier and Bohidar, and in view of Tischer, Desai, and Bangs, respectively.

The examiner admits that Vaynberg does not specifically recite a buffer of pH 10.5 to 12.5 but rather teaches adsorption of gelatin onto particles at pH values up to pH 10 (Figs. 1-7). The examiner argues that it would have been obvious for one of ordinary skill in the art to employ slightly higher pH values through routine optimization/experimentation of the conditions of Vaynberg with a reasonable expectation of success. She argues further that one would be motivated to employ higher pH values because Vaynberg teaches that because hydrophobic effects dominate in adsorption of gelatin, increasing pH results enables a denser layer of gelatin to form on the polystyrene (p. 470, left column, first full paragraph). Finally, the examiner argues that one would have reasonable expectation of success in employing higher pH values in the method of Vaynberg because Vaynberg teaches that pH differences were not critical and produced little variation in the adsorption efficiency of gelatin onto the polystyrene (p. 469, right column, l. 25 to p. 470, left column and Figs. 2-3). The examiner points out that, in particular, Vaynberg teaches that "pH hardly affects the adsorption of gelatin" and "the ability of gelatin to adsorb to [polystyrene] even at high electrolyte and high pH conditions"

Applicants traverse the rejection and argue that the examiner's case for *prima facie* non-obviousness has not been made. Applicants argue firstly that Vaynberg does not motivate the skilled artisan to assess coatings at pH values higher than 10. Vaynberg explicitly teaches that the maximum adsorption is around pH 6.2 for coating of polystyrene particles (p. 469, left column, l. 5-7). With this explicit teaching of an adsorption maximum, Applicants argue that there is clearly no motivation for the skilled artisan to test the pH range beyond the broad range of pH values already tested by Vaynberg. Further, Vaynberg teaches the numerous methods and conflicting results that have been taught by the prior art (page 466, left column, 3rd paragraph through page 467,

left column, 2nd paragraph). In particular, Cosgrove et al. (Langmuir 14:5376-5382, 1998) studying gelatin adsorption to polystyrene colloids found that gelatin coverage and layer extent decreased with increasing pH above the isoelectric point. Vaynberg concludes that general trends and predictions for gelatin adsorption are difficult to extract from the data reported in the literature.

The examiner has characterized the pH range of the claimed invention (10.5 to 12.5) as "slightly higher" than the maximum pH value attempted by Vaynberg. However, Applicants point out that a pH of 10.5 is 5 times more alkaline than a pH of 10, not just "slightly" more alkaline. The examiner also points out that MPEP 2144.05 notes that:

> "...a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties."

Indeed, increasing alkalinity by 5 times more than the greatest alkalinity tested by Vaynberg in light of Vaynberg's teaching that the maximum adsorption is around pH 6.2 for coating of polystyrene particles would hardly be expected by the skilled artisan to result in "the same properties".

The examiner also has argued for a reasonable expectation of success using higher pH values than used by Vaynberg; however, Applicants argue to the contrary that the skilled artisan would have no reasonable expectation for success by increasing the pH significantly beyond the maximum pH tested by Vaynberg. First, it should be pointed out that in Vaynberg's studies, the only instance in which pH 10 was employed is that illustrated in Figure 8 in which the thickness of the gelatin layer as a function of pH was observed, and that steady increase in layer thickness was attributed by Vaynberg to swelling of the layer with increased pH, which is what is reported for free gelatin in solution. This experiment does not indicate that more gelatin has adsorbed to the surface of the polystyrene. Figure 2 shows equilibrium adsorption constants on polystyrene (and acrylic latex) as a function of pH, and the highest pH shown is pH 9. Figure 3 should entropy of gelatin adsorption on polystyrene and acrylic, and again, the highest pH

shown is pH 9. Figures 4 and 5 likewise only show results us to pH 9. In Figure 7, which the examiner specifically points out, the pH's reported are 5.7, 6.6, and 8.8. Thus, arguments regarding Vaynberg's teachings should not be extrapolated beyond the pH values actually tested and reported by Vaynberg.

Applicants further argue that, as the skilled artisan recognizes, the use of higher pH values increases the risk of irreversible protein denaturation by alkaline hydrolysis.

In conclusion, Applicants argue that the teachings of Vaynberg do not render the present invention obvious, and the teachings of the Bocquier, Bohidar, Tischer, Desai, and Bangs references do not make up for the deficiencies of Vaynberg. Vaynberg does not provide the motivation for the skilled artisan to attempt a pH higher than those studied by Vaynberg and the rest of the prior art. Furthermore, the skilled artisan would not have a reasonable expectation of success were he to even try.

With regard to the rejection of claims 2, 3, and 5, Applicants argue that these claims depend from claim 1 and should enjoy the patentability of claim 1 as argued above.

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection of claims 1-3 and 5 under 35 USC §103 (a) is respectfully requested by Applicants.

Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above amendments and remarks is respectfully requested. Allowance of claims 1-3 and 5 at an early date is earnestly solicited.

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The examiner is hereby authorized to charge any fees associated with this Amendment to Deposit Account No. 02-2958. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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